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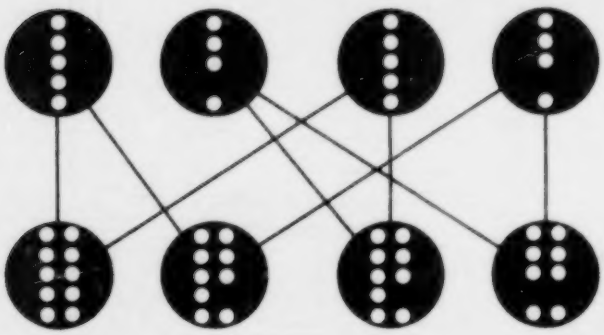
A PARENT'S GUIDE TO CYSTINOSIS



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Prepared by Stephen P. Spielberg, M.D., Ph.D.
Ann McNemar, R.N.
National Institute of Child Health and Human Development
National Institutes of Health
Bethesda, Md. 20205

Cystinosis is a rare disorder. In the United States, only a few hundred children have cystinosis. With a patient population so widely scattered it is not easy for parents to be in touch with one another for practical and moral support. Soon after diagnosis, parents are confronted with new medical terms, medicines, and genetic counseling. It is often easy to become confused, and forget or misinterpret some of the information about the day-to-day care of their child. This booklet reviews some of this information, using and defining the medical terms that are apt to come up in conversation with the child's doctor. It is based in part on questions raised by the parents of children with cystinosis. It also contains suggestions they have for other parents.

WHAT IS CYSTINOSIS?

Cystinosis is a genetic or inherited disease. It is caused when a substance called cystine builds up in the body tissues. Cystine is found normally in the body but in smaller amounts than in cystinosis. It is an amino acid, a building block for protein. Why it accumulates in the body is not known, but certain things are known not to cause the disorder. Nothing that a mother or father does or does not do before or during pregnancy causes cystinosis, nor is it caused by anything connected with an infant's care or diet. The disease is present at birth even though it is usually not apparent in the first months of life. Diagnosis often is not made, in fact, until after a year or a year-and-a-half, when the symptoms first appear.

HOW IS CYSTINOSIS DIAGNOSED?

A variety of signs and symptoms can lead to diagnosis. A child's growth may be slow. Or a child may begin to drink and urinate more than usual, or to crave salt. The child may avoid bright light—a tendency hard to notice, however, in the small infant. Routine urinalysis may show sugar or protein in the urine and prompt other tests. Or the child may come to a hospital with dehydration (loss of body water) and be given tests of kidney function that suggest an abnormality.

Diagnosis can be made with an eye examination (by an ophthalmologist) which will show cystine crystals in the cornea, the front part of the eye and mild changes in the retina, the back part of the eye. Tests of kidney function, and a blood test that measures the cystine content of the white blood cells, confirm the diagnosis.

WHAT ORGANS ARE AFFECTED?

All of the problems that arise in cystinosis are believed to come from cystine accumulating in the body tissues. Some organs are affected more than others.

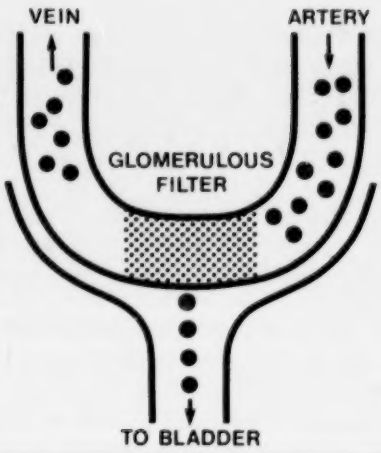
The kidney

The kidney is the area of most concern in cystinosis. The kidney can be viewed as having two functions: (1) to filter waste products from the blood and (2) to reabsorb from the filtered fluid the water and other substances needed to maintain the body's chemical balance. The filter function is not significantly damaged in the early years of cystinosis but the reabsorption function is, and treatment is aimed at replacing the substances lost in the urine.

Picture 1 is a representation of a normal kidney. Waste products are filtered from the blood. Then water plus salt, potassium, bicarbonate, phosphorus, sugar and some protein, along with the waste products, pass into the kidney tubules. The tubules then reabsorb most of the water and the salt, potassium, bicarbonate, phosphorus, sugar and protein, and return them to the blood. The waste products and a small amount of the filtered water pass down through the tubules and into the bladder as urine.
Early in the course of the disease, the tubules lose their capacity to reabsorb the water and other substances (see picture 2). This condition is called Fanconi's syndrome. It is because water is being lost in the urine, instead of reabsorbed by the tubules, that children with cystinosis have to drink and urinate so often.

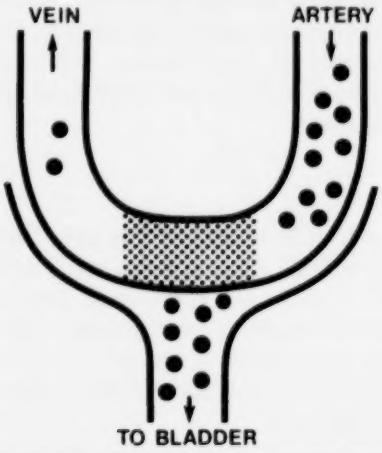
The amount of sugar and protein lost in the urine is actually very small, and no replacement treatment is re-

1 NORMAL

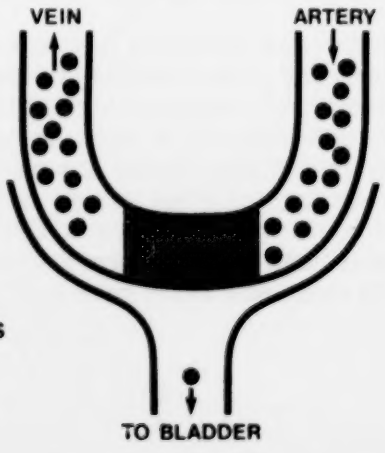


2 EARLY CYSTINOSIS

FANCONI'S SYNDROME



3 LATE CYSTINOSIS



● WASTE PRODUCTS

● SALT, WATER, POTASSIUM, ETC.

quired. The water, salt, potassium, bicarbonate and phosphorus, on the other hand, may have to be replaced. All of these substances are important. For example, phosphorus is present in bones as well as blood, in a balance with calcium and magnesium. When it is lost in the urine in cystinosis, the balance of these three substances in the bones is sometimes altered enough to cause a bone disease called rickets. Rickets is discussed later.

The kidneys' second function, that of filtering waste products from the blood, also is damaged in cystinosis. The process is much more gradual, however. Picture 3 shows how the damaged filter finally allows waste products to accumulate in the blood and remain there. When this happens, the child is said to have kidney or renal failure. It occurs at different ages, but usually between 9 and 12 years. Treatment of renal failure, which includes dialysis (with an artificial kidney machine) and kidney transplant, is discussed later.

The eye

Although cystine is found in the eye, there is no loss of vision in cystinosis. Children do not become blind from the disorder, and do *not* have even partial loss of vision. They are apt to be sensitive to bright light, and may want to wear dark glasses or a hat on very bright days. They also may be uncomfortable having their pictures taken with a flash camera.

Other tissues

One other organ can develop a problem: the thyroid gland. Children with cystinosis can become hypothyroid (have too little thyroid hormone in their blood). The condition is easily detected with a blood test and can be treated (with thyroid pills) before any symptoms appear. Cystine accumulates in other tissues of the body but generally without impairing function. Cystine collects in the liver, but usually no significant liver disease results. Children with cystinosis often have light hair and skin color.

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HOW ARE GROWTH AND DEVELOPMENT AFFECTED?

Children with cystinosis grow more slowly than other children. Why this is so is not completely understood. Even when they are getting a good diet and their blood levels of various chemicals are being corrected with medicines, the children tend to remain short. It is hard to predict how tall a child with cystinosis will be at any given age, but your child will probably be the shortest in his class. His body proportions and facial features will be entirely appropriate for his size.

Because cystine does not accumulate in the brain, children with cystinosis are not retarded. They learn and develop normally.

HOW DOES A CHILD GET CYSTINOSIS?

People have 46 chromosomes, two sets of 23, in their cells. In other words, everyone has two number 1 chromosomes, two number 2 chromosomes, and so on. One set (one number 1, one number 2...) comes from the mother, the other from the father. (Eggs and sperm have only one set, but the cells of the baby produced when they join contain 46 chromosomes.)

A chromosome can be viewed as a string of beads, each bead representing a gene. Each gene, it could be said, controls a different function in the body. Because chromosomes come in pairs, we have two genes (one from each parent) for each function. Everyone has several abnormal genes (an average of five to seven) which can cause a variety of diseases, but these are not expressed (do not produce disease) if the paired gene on the other chromosome is normal. A gene that is not expressed is called recessive; a person who has that recessive gene paired with a normal gene is called a carrier.

How, then, can a recessive gene be expressed as a disease? The child must inherit the recessive gene from each parent to have the disease. As we have said, eggs and sperm each contain one set of 23 chromosomes. When joined, they produce cells containing 46 chromosomes. Here, a black bead is the recessive gene on one chromosome in each parent's cells (picture 4); as eggs and sperm cells are made, each gets one set of chromosomes. There are an equal number of eggs and sperm made containing the normal and the abnormal gene (picture 5). The eggs and sperm meet randomly, with only three possible results (picture 6).

Thus, the chances are one in four that the child of two people who are carriers will be entirely normal (have two normal genes); two in four that he will be a carrier (have one normal and one abnormal gene), and one in four that he will have the disease (have two abnormal recessive genes).

With each pregnancy there is one chance in four that parents carrying the disease will have an affected child, and three chances in four that they will have a normal

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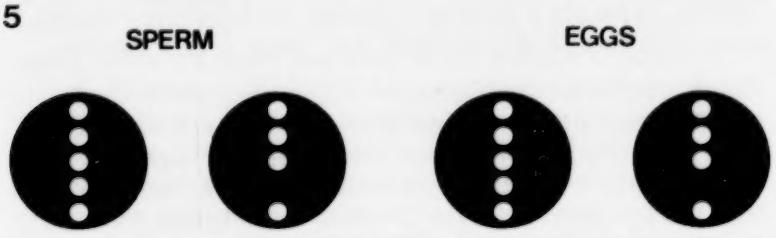

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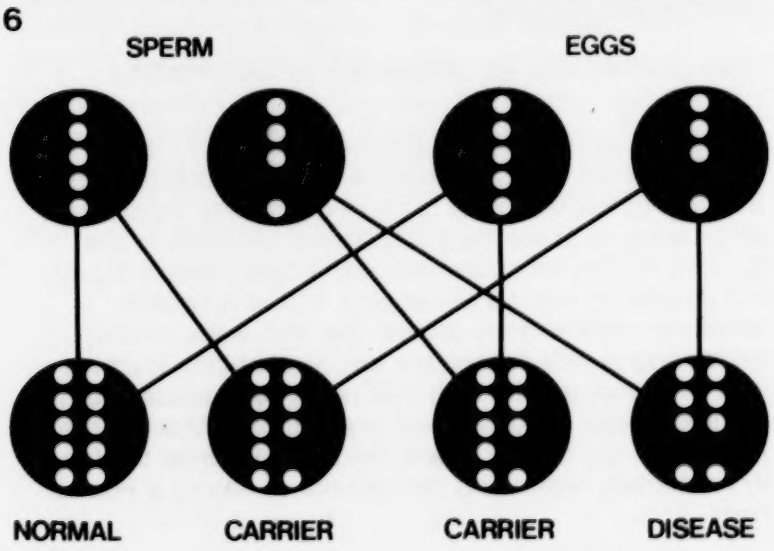

child. (This normal child, of course, has two chances out of three of being a carrier just like the parents.) The outcome for one pregnancy does not change the odds for future pregnancies.

Cystinosis is one of these recessively inherited diseases. Thus, for a child to be born with cystinosis, both of his parents must be carriers of the gene for cystinosis. And, the chances are one in four—with each pregnancy—that a child of these parents will have the disorder. There is no screening test to determine that parents are carriers before they have a child with cystinosis. Everyone is a carrier of a number of abnormal genes and appears entirely normal because the genes are recessive.

The chance is very small that a second member of the family—a parent's brother or sister, for example—would also carry the gene and meet and marry another carrier.

Relatives can be checked by a blood test, which can sometimes determine whether or not they are carriers. If they have children who are several years of age with no symptoms of cystinosis, they need not be concerned that the children may later develop the disease. However, genetic counseling may still be advisable for relatives of patients and carriers.

CAN CYSTINOSIS BE DETECTED IN AN UNBORN CHILD?

Cystinosis can now be diagnosed before birth, by a process called amniocentesis. A needle is placed into the fluid surrounding the fetus (the amniotic fluid) and a small amount of the fluid withdrawn. The cells in the fluid are tested for cystinosis and if cystinosis is found, the pregnancy can be terminated, if that is desired. Amniocentesis is done around the 16th week of pregnancy and is safe for mother and fetus. Many mothers who have had a child with cystinosis have made use of amniocentesis in subsequent pregnancies. Most of the time (three out of four times) the test will show the fetus to be normal, reassuring the parents of having a normal baby.

WHAT IS THE TREATMENT FOR CYSTINOSIS?

The first treatment for cystinosis consists of correcting with medicines any abnormalities in sodium, potassium, bicarbonate, calcium, and phosphorus that may exist at the time a child is diagnosed. These things are usually corrected gradually, because it takes some time to find the right dose for each medicine that a child needs. Once the proper dose of medicine is found, the goal is to maintain blood chemistries as close to normal as possible. This requires periodic blood tests to check how much sodium, potassium, and so forth are in the blood.

Water

Because their kidneys cannot reabsorb water adequately after it is filtered from the blood, children with cystinosis have to urinate and drink with great frequency. They need to have liquids available at all times, including at night. A bottle of Pedialyte (a commercial solution of water, salt and sugar) or iced drinks—cola or gingerale—or simply a glass of ice can be kept by the bed. Non-carbonate drinks can be kept cold in the child's room in a thermos bottle.

Because of the high volume of urine in cystinosis, the children can have problems with toilet training, particularly in staying dry at night.

Usually, however, they soon adapt to getting up to urinate, sometimes using a potty in the room. In time they learn to stay dry throughout the night. To restrict water does not help and to do so can cause dehydration, particularly in the younger child.

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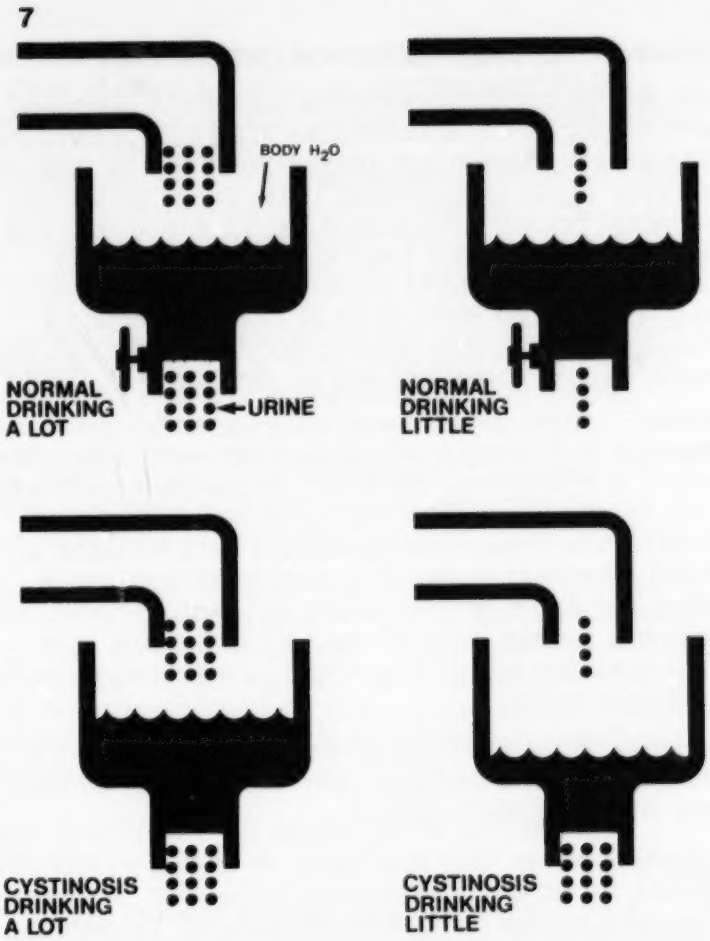

A normal kidney maintains a constant level of water in the body by regulating the amount of urine produced. As in the tank shown in picture 7, the more we drink, the more urine we make. If we drink less the kidney acts like a valve and makes less urine, keeping the amount of water in the body constant. In cystinosis, the kidney is like a tank without a valve; if a child drinks less, the volume of urine remains high while body water falls, leading to dehydration.

Dehydration can be a serious problem in cystinosis. This can happen if a child's intake of fluids is less than his

output (in not only urine, but with sweating, vomiting, and diarrhea). Weight loss is a good measure of water loss in dehydration. A child who loses 5 percent of his body weight in a short time—say, in 24 hours—is well on his way to becoming dehydrated; this would mean, for example, a 20-pound child losing 1 pound. To monitor weight loss, it is a good idea to have an accurate scale at home.

Other signs of dehydration are a dry mouth, decreased tears, and a tired and generally ill appearance. Any young child with cystinosis who has vomiting or diarrhea, or who is not drinking and taking his medicines for any reason, should be seen by his doctor within several hours. With experience parents usually can gauge when a problem is becoming serious, but soon after diagnosis close contact with the doctor is very important. Here are some tips for managing fluid loss in diarrhea and vomiting:

- Milk and solid foods are stopped, and fluids and medicine are stressed. If a child is vomiting, clear liquids such as Pedialyte, flat cola, apple juice and liquid gelatin can be used.
- A child is more likely to keep things down if he is given small, frequent sips rather than a whole glass at a time.
- If medicines are vomited within ½ hour after being taken, they should be repeated. (This may vary with the medicines, and you should check with your doctor.) The dose may be divided into smaller amounts and given several times over ½ to 1 hour, rather than all at once.

If a child does become dehydrated, his doctor needs to treat him with intravenous fluids to rebalance the water, salt, and other minerals.

Diet

Children with cystinosis need a special diet. As with any child, their likes and dislikes vary from time to time, even from day to day, and their appetite will fluctuate too. Trying to stuff a child with food will not make him grow faster—and more often than not it makes mealtime difficult. Appetite will often increase when the blood chemistries have been corrected. The child's need to drink will

sometimes interfere with his appetite for solid food, and he may sometimes get somewhat fewer calories than he should. In general, a child needs to be encouraged to do most of his drinking between meals, and he is likely to eat more at mealtime if he is allowed only a moderate amount to drink, one to two cups, depending on age. Liquids that have calories, like milk, fruit juices, and regular sodas, have an advantage over water or diet soft drinks. Pedialyte also has some calories. If your doctor or dietitian suggests further increases of calories in solid foods, you can use butter, gravies, sauces, or other high calorie foods whenever acceptable to your child. Mealtimes are easier when your child learns as much as possible to eat what the rest of the family is eating.

Medicines

Giving medicines to a child is often a difficult task for parents—especially soon after diagnosis, when so many new medicines may be started and doses are changed frequently.

Children with cystinosis will always require some medications to replace the substances lost in urine. Fortunately, as with other children who require medicines over long periods of time, they adapt to taking their medicines. It becomes a more or less routine "fact of daily life." Here are some hints on giving medicines:

- Write down the names and doses of the medicines and at what time of day they are to be given. A daily calendar helps at the beginning.
- Be sure you fully understand your doctor's instructions. Some medicines can be given with meals and mixed with foods or liquids, others cannot; some can be given together with other medicines, and others cannot. A daily list really helps to organize this.
- Many of the medicines are liquids and have to be given in exact amounts. Measuring doses with a syringe or measuring cups helps, and your doctor or nurse can show you how to use them properly. Teaspoons vary so much in size that it is best to use a standard measure.

Some of the medications your child may be given are listed below. No two children with cystinosis have the same needs, so your child may receive different medi-

cines than another child the same age. This does not mean that he is more or less ill than another child. A child's needs for the various medicines are checked periodically by blood tests, most of which can be done by your doctor.

Salt and potassium—Some children with cystinosis crave salt (sodium chloride), and their desire for it can be a fairly good guide to their needs. In any case, salt should not be restricted in their diet. Some children require additional supplementation with salt tablets at recommendation of a physician.

Potassium can be provided in the form of potassium chloride, potassium phosphate, Polycitra, or several other forms. Foods high in potassium include oranges, tomatoes (and their juices), bananas, cantaloupe, peas, carrots and leafy green vegetables. A child's potassium requirements must be very carefully monitored. Potassium loss may increase with vomiting and diarrhea, and since very low potassium is dangerous, blood tests during an illness are important.

Bicarbonate—The "acid-base balance" of the body is easily disturbed in children with cystinosis because bicarbonate is lost in the urine. The body does not function well when blood is too acid. Acidosis (too much acid in the blood) can be corrected with sodium bicarbonate, Polycitra (a mixture of potassium and sodium citrate, the citrate changing to bicarbonate in the body), or Shohl's solution, which is similar to Polycitra. A child's need for bicarbonate may go up during any illness with fever. A blood test will show he is getting enough. One sign of acidosis is deeper, more rapid breathing.

Of all the medicines a child takes, potassium and some form of bicarbonate are probably the ones most vital for him to have with great regularity. Both of them are easily and rapidly lost in cystinosis, so to miss taking the replacement medicines is dangerous. If you are having trouble getting your child to take his medicine on a given day because he is so sick or just "having a bad day," it is best to concentrate on helping him get his potassium and bicarbonate.

Calcium and phosphorus—As indicated earlier, the loss of chemicals in the urine can alter the balance of calcium, phosphorus, and magnesium in bones as well as blood and lead to rickets, a bone disease. Bones with rickets do not grow well, are "softer" than normal, and can break easily. To see if rickets is present, a doctor needs to x-ray the bones and measure calcium, magnesium and phosphorus in the blood. To treat the condition, the medicines containing the three substances are adjusted to restore them to the blood in proper balance. Sometimes vitamin D is given instead, or in addition. Vitamin D helps the stomach absorb calcium and helps bone to use these substances to correct and prevent rickets. A child may need much more vitamin D than can be provided in his diet. Proper treatment eventually heals the rickets and can help prevent its recurrence. Once a child is treated, his activity need not be restricted.

In addition to rickets, the loss of blood calcium or magnesium can cause tetany. A child with tetany may first develop cramping in the muscles of his legs, hands or feet. This can become severe, leading to general muscle cramping and even convulsions. Tetany can be prevented by maintaining blood calcium and magnesium at the proper levels. If a child develops cramping in his legs, arms, hands or feet, he should be seen by a doctor.

Problems with tooth decay, which sometimes develop in cystinosis, also may relate to the child's calcium and phosphorus metabolism. Good dental hygiene and dental check-ups are essential.

WHAT ABOUT A CHILD'S CARE AT SCHOOL?

Most schools ask parents to fill out some kind of health information form so the school can know about any health problem a child may have, and be prepared to help. For example, your child's teacher must know that the child must go to the bathroom often and also drink often.

Medicines—Ideally, your child's medicine schedule can be arranged so he can take all his medicines at home. There are several alternatives if this is not possible. If your child takes a lunch, it may be possible to include a

single does of one or more medicines so he can manage for himself. If he needs help, on the other hand, a school nurse sometimes is available. If the nurse is not in school every day, arrangements often can be made for a teacher to help. In any case, if someone at school will be helping, the medicine must be put in a bottle labeled with your child's name, the name of the medicine, the dose, and the time for giving it. The school may ask that the doctor authorize the school in writing to administer the medicine.

Short stature—Children with cystinosis are bound to have some problems with the school's physical makeup. Toilets, storage areas, blackboards and pencil sharpeners all will be high, and the situation becomes increasingly troublesome as the child progresses to the upper grades.

Short stature also can interfere with play activities. When a child is undersized, he sometimes is babied just when he needs to be encouraged to do things on his own. He may also be bullied. Parents can anticipate situations like these and help the child cope with them. It helps to meet with a child's teacher occasionally to compare notes on his behavior at home and at school and share ideas about how to help him do his best. Above all, he needs to be allowed to participate and play. His teacher should understand from the very beginning that cystinosis in no way interferes with normal learning capacity.

Discipline—Occasionally a child with cystinosis needs to miss some school because of illness. Children with a chronic disorder sometimes try to use it to avoid school and other responsibilities. In time, parents will come to know how their child really feels, and how to balance medical concern, discipline and encouragement to help him to grow and mature. Like every child, he needs to have guidelines and discipline so he can develop and gain a sense of who he is. Not to provide this kind of discipline can only hurt him in the long run, and can create serious problems for other children in the family as well.

HOW IS THE KIDNEY FAILURE TREATED?

As described earlier, the kidney's filter function is lost gradually, over a number of years, and the outcome is kidney failure. It happens at different ages, but usually between 9 and 12 years. The condition of the kidney can be checked with blood and urine tests that measure creatinine and blood urea nitrogen (BUN). When a chld is approaching kidney failure, his blood can be "cleaned" with an artificial kidney machine. The process is called dialysis. It can be used until a suitable kidney transplant is found for the child, and it can be continued for years. The new kidney does not "get" cystinosis and it functions as well as any other transplanted kidney. After kidney transplants, so far as is now known, cystinosis does not cause new problems for other organs.

WHAT ARE THE EMOTIONAL ISSUES?

Learning that a child has a chronic illness like cystinosis is never easy for parents. Often at the beginning parents find it hard to believe the diagnosis; families think that there must be some mistake, or that the problem will go away. Sadness and anger become mixed and leave parents confused or even frightened by their feelings. It is not unusual to be angry that the diagnosis was not made sooner, or for one parent to blame the other for being "responsible." (Both parents, of course, are carriers.) Even after the facts are explained, many of these feelings may linger on, and may be difficult to cope with at times. Probably everyone asks, "Why my child?"

After parents accept the diagnosis, questions arise such as "How should I act toward my child?" This can be a particularly hard issue in dealing with a child with cystinosis, who has normal intelligence for his age but who is also very small and has some special needs because of his disease. Parents may wonder, "How protective should I be?" or "Am I being overprotective?" There is no right or wrong way to deal with a child who has cystinosis, nor a right or wrong way to handle one's emotions when faced with a problem like this one. Everyone has a different "style," a different way of coping. Children with cystinosis go through the same stages

of development as other children, and their parents know the same excitement watching them grown, the same frustrations, anger and disappointments that other families know. As with all children, there is the same need for discipline and for setting limits. There is also the same need for parents to have time to themselves and time for other members of the family.

Parents have often found it helpful to talk among themselves, sharing their common concerns as well as helpful tips they have learned over time. It usually is of great help too, to discuss some of these concerns with the doctors, nurses and social workers involved in the care of the child.

WHAT IS RESEARCH DOING ABOUT CYSTINOSIS?

Part of the ability to cope with cystinosis comes from knowing that one is not alone in dealing with the problem, that there are other families experiencing similar difficulties and that there are groups of doctors and scientists all over the world who are doing research into the causes and possible cure of cystinosis. Scientists still do not know what causes cystinosis at the cellular level, and much work needs to be done. The aim of research is to understand why cystine accumulates in cells, and then to find ways of either preventing the accumulation or removing the cystine once it is present to prevent damage to tissues of the body, particularly the kidney.

Many studies are underway, looking at what effect drugs have on cystine found in skin cells grown in special "culture dishes" in the laboratory. These cells can be grown from a small "biopsy" (a piece of skin taken from the arm of a patient with cystinosis). Tests are done on these cells looking for drugs that might be useful in treating cystinosis. When a drug is found that decreases a cell's cystine content, and the drug's safety is checked, it can then be studied in a "clinical trial" under careful medical supervision to see if it can help children with cystinosis, and is safe over the long term. Studies are now in progress in the United States, and elsewhere, and new advances are rapidly communicated to doctors caring for children with cystinosis.

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